REMARKS

Claims 3-10, 13-16, 18, 19, 21-26 and 29-32 were pending. Claims 3-10, 13-16, 18, 19, 21-23, 25, 26 and 29-32 were examined.

Claims 3-10, 13-16, 18, 19, 21-26 and 29-32 are cancelled without prejudice, and the subject matter of these claims re-presented as new claims 33-64.

Support for new claims 33-64 is found throughout the specification, with specific support detailed below.

New Claims	Exemplary Support in the Specification
33	original claims 3 and 12; page 4, lines 16-35
34-38, 55-59	page 8, line 30 - page 9, line 12
39	original claim 5
40	original claim 8
41, 42	page 5, lines 8-14
43	original claim 7
44	original claim 9
45	original claim 10
46, 47	original claims 14 and 15
48	original claims 6 and 15
49, 50	page 4, lines 20-28
51-53	original claim 13
54	original claim 16
60	original claim 18
61	original claim 21
62	page 4, lines 31-35
63	original claim 22
64	original claim 23

Thus, the new claims do not constitute new matter. This amendment is made to more clearly define the invention and solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter.

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Claim objections

Claims 4, 13, 19, 25, 29, 30 and 32 were objected to because of term informalities.

Applicants have addressed these objections in the amended claims and respectfully request withdrawal of these objections.

Rejections under 35 U.S.C. §112, first paragraph

Claims 3-16, 18, 19, 21-23, 25-32 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled. Applicants respectfully traverse these rejections, to the extent that they are applied to the amended claims.

The Examiner's concerns are essentially related to effective "scope" of the enablement. The Examiner asserts that specification "does not enable using any cell or combination of cells expressing any therapeutic molecule to treat any disease" (Office Action, page 5, section 2). Applicants submit that the invention is not as broadly claimed as the Examiner asserts.

The claimed invention is directed to methods of treating a disease responsive to a biologically active molecule in a mammal through creating an immune-privileged site in the mammal by administering retinal pigmented epithelial (RPE) cells and co-administering a second cell population to the site. The second cell population supplies the biologically active molecule to the mammal and is allogeneic to the mammal. The claimed invention is also directed to pharmaceutical compositions and kits comprising RPE cells and a second cell population in which the second cell population produces a biologically active molecule that is absent or defective in a disease and the second cell population is allogeneic to the RPE cells.

The specification provides examples of diseases responsive to a biologically active molecule as well as examples of therapeutic biologically active molecules and examples of cells

which produce such molecules (see, for example, page 4, lines 28-35; page 5, line 27, to page 6, line 2; page 6, line 35, to page 7, line 2; page 8, line 32, to page 9, line 12). In addition, diseases responsive to administration of specific biologically active molecules and cells that produce the specific molecules were known in the art.

The Examiner acknowledged that Langerhans cells "can be used to treat diabetes upon transplantation and adequate secretion of insulin" but finds that the specification does not support using Langerhans cells "to secrete any other therapeutic molecule" (Office Action, page 6, section 2). Solely to promote prosecution, pending claim 63 is directed to kits comprising insulin-producing pancreatic islet of Langerhans cells.

Accordingly, Applicants submit that the pending claims fall within the subject matter that is enabled by the specification.

The Examiner further asserts that the specification does not provide any guidance regarding administration of cells *in vivo* and specifically, no guidance on "how to use pancreatic islet of Langerhans cells" (Office Action, page 5, section 2).

The specification describes administration of the cells of the invention (see, for example, page 15, line 11, to page 16, line 14) and indicates that administration of these cells is accomplished by conventional techniques. *In vivo* administration of the cells of the present invention was well-known in the art at the time of filing.[1] Also, it was well-known in the art and acknowledged by the Examiner, as noted above, that pancreatic islet of Langerhans cells are transplanted to treat diabetes. Accordingly, with regard to cell administration, Applicants submit that the pending claims fall within the subject matter that is enabled by the specification.

With regard to the rejection of claim 5, claim 5 was directed to the claimed method wherein cells of the second cell population are transformed by a nucleic acid encoding the biologically active molecule. Thus, the biologically active molecule of claim 5 is one encoded

[1] For example, references of record (Ye et al. and Cherksey) describe administration of RPE cells to mammals and references mailed with the instant Office Action describe implantation of islet of Langerhans cells into mammals. See Sigalla et al. (1997) *Human Gene Therapy* 8:1625-1634; Weber et al. (1997) *J. Surg. Res.* 69:23-32.

by a nucleic acid. Accordingly, Applicants submit that the pending claims fall within the subject matter that is enabled by the specification.

With regard to claim 22, the Examiner asserts that the "specification does not provide a written description regarding how to use a kit comprising pancreatic islet of Langerhans cells and RPE cells" (Office Action, page 7, section 3). Applicants respectfully traverse this rejection, to the extent that it is applied to the amended claims.

The specification describes the use and administration of RPE cells to create an immune-privileged site in a mammal and the co-administration of a second cell population that supplies a biologically active molecule. As discussed above, it was well-known in the art how pancreatic islet of Langerhans cells can be administered to supply insulin to a mammal. See, for example, footnote 1.

Thus, Applicants submit that the pending claims fall within the written description requirement of the specification.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request that the rejection of claims under 35 U.S.C. §112, first paragraph, be withdrawn, to the extent that they are applied to the amended claims.

Rejections under 35 U.S.C. §112, second paragraph

Claims 3-7, 9-16 and 19 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse these rejections, to the extent that they are applied to the amended claims.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have

attempted to incorporate and/or respond to each of the various suggestions of the Examiner in order to enhance clarity and to facilitate disposition of the present case. Applicants welcome any additional suggestions the Examiner may have and would appreciate the opportunity to discuss the claims with the Examiner after he has had an opportunity to review this Amendment and Response in order to ensure that the case can be placed in condition for allowance.

The Examiner has asserted that claim 3 was indefinite "because it is unclear whether applicants intend to administer RPE cells alone or RPE and non-RPE" and "it is unclear whether the cells are administered simultaneously" (Office Action, page 7, section 4). The method of the present invention comprises administering RPE cells and co-administering a second cell population to the same site. Applicants submit that the specification is clear to one skilled in the art that the co-administered second cell population is made of cells other than unmodified RPE cells and have addressed this concern below with the rejections under 35 U.S.C. §102. The Examiner acknowledges that the specification states that co-administration can be in a single composition or as separate compositions. Thus, the specification provides for methods comprising administration of the RPE cells and the second cell population that delivers molecules not normally produced by RPE cells at the same time as well as administration of the two cell populations at different times.

Accordingly, Applicants respectfully request that the rejection of claims under 35 U.S.C. §112, second paragraph, be withdrawn, to the extent that they are applied to the amended claims.

Rejections under 35 U.S.C. §102

Claims 3, 4, 7, 9, 13, 16, 19, 25, 29, 30 and 32 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Ye et al. (1993, *Current Eye Research*, 12:629-639) ("Ye"). Applicants respectfully traverse this rejection.

The present invention is directed to methods for treating a disease responsive to a biologically active molecule in a mammal by creating an immune-privileged site in a mammal by administering an effective amount of RPE cells and co-administering to the site a second cell

population that supplies an effective amount of the biologically active molecule. In the claimed methods, the second cell population is allogeneic to the mammal. Pending claims are also directed to compositions comprising RPE cells and a second cell population, wherein the second cell population produces a biologically active molecule. In the claimed compositions, the second cell population is allogeneic to the RPE cells.

The Examiner asserts that the "definition of the co-administration of cells as defined in the specification encompasses RPE alone" (Office Action, page 10, section 5). Applicants disagree with this definition of the co-administered cells, *i.e.*, the second cell population, in the present invention.

The specification clearly describes embodiments in which RPE cells are administered with a second type of cell. For example, on page 6, line 36, the specification states that "RPE cells are co-administered with additional cells or tissues, such as neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecules". Further, on page 12, line 16, the specification refers to "transplanted RPE cells or co-administered cells" (emphasis added). Thus, the specification clearly distinguishes between RPE cells and the co-administered cells. Therefore, from the specification, it is clear that the co-administered cells are not RPE cells.

Applicants submit that meaning in the claims cannot be contradictory to the specification. Courts decisions have held that words defined in the specification should be given the same meaning in the claims. See Fonar USPQ2d 1109; McGill, 736 F.2nd 674, 221 USPQ 949; Autogiro, 384 F.2nd 397, 155 USPQ 702-703. Accordingly, Applicants submit that the pending claims are not directed to methods administering RPE cells alone.

Ye describes transplantation of allogeneic RPE cells to the retina of rabbits. Ye does not teach administering RPE cells and co-administering a second cell population to a mammal, much less co-administration of RPE cells with a second cell population, wherein the second cell population supplies a biologically active molecule not normally produced by RPE cells and

wherein the second cell population is allogeneic to the mammal. Thus, Ye does not teach the claimed invention and, accordingly, Ye does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b), to the extent that they are applied to the amended claims.

Claims 3, 4, 6, 7, 9, 10, 13, 16, 18, 19, 21, 23, 25, 26, 29, 30 and 32 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Cherksey (U.S. Patent 5,618,531) ("Cherksey"). Applicants respectfully traverse this rejection.

Cherksey describes neural or paraneural cells, including RPE cells, attached to a matrix and administered to the brain for the treatment of Parkinson's Disease. Cherksey also describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6).

Contrary to the Examiner's assertion, Cherksey does not teach or suggest that the glial cells co-incubated and implanted with neural or paraneural cells are allogeneic relative to the animal recipient and/or relative to the neural or paraneural cells. Cherksey is silent with regard to the relationship of the glial cells to the neural or paraneural cells and/or to the animal recipient. In fact, the Examiner admits that "Cherksey does not teach that the co-culture of cells is allogeneic" (Office Action, page 11, section 7).

Thus, Cherksey does not teach the claimed methods of the invention, *i.e.*, administering RPE cells and co-administering a second cell population to a mammal, wherein the second cell population supplies a biologically active molecule and wherein the second cell population is allogeneic to the mammal. Also, Cherksey does not teach the claimed compositions comprising RPE cells and a second cell population, wherein the second cell population is allogeneic to the RPE cells and wherein the second cell population supplies a biologically active molecule that is absent or defective in a disease.

For a claim to be anticipated by a reference, that reference must disclose each and every element of the claim. Cherksey does not teach the claimed invention. Accordingly, Cherksey does not effectively anticipate the present invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e), to the extent that they are applied to the amended claims.

Rejections under 35 U.S.C. §103

Claims 3, 14, 15, 16, 18, 19, 21, 23, 29, 31 and 32 were rejected under 35 U.S.C. §103 as allegedly being unpatentable over Cherksey. Claims 3, 5, and 8 were rejected as allegedly being unpatentable over Cherksey in view of Goldstein et al. (U.S. Patent 5,300,436) ("Goldstein"). Applicants traverse these rejections.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

The present invention relates to the use of RPE cells to create an immune-privileged site upon administration to a mammal. The immune-privileged site created by the RPE cells allows for the co-administration of cells which are allogeneic to the mammalian recipient of the cells. Thus, the methods of the present invention comprise co-administering RPE cells and a second cell population to a mammal in which the second cell population is allogeneic to the mammal. Pending claims are also directed to compositions and kits comprising RPE cells and a second cell population, wherein the second cell population is allogeneic to the RPE cells.

Cherksey teaches administration of matrix-attached neural or paraneural cells, including RPE cells, to the brain. As discussed above, Cherksey also describes "co-culture of neural or paraneural cells with glial cells." The Examiner acknowledges that "Cherksey does not teach that the co-culture of cells is allogeneic" but states that "Cherksey teaches that the cells of the instant invention may be allogeneic to the host (column 11, line 37)" (Office Action, pages 11-12, section 7). As outlined above, Cherksey is silent with regard to the relationship of the glial cells to the neural or paraneural cells and/or to the animal recipient.

Cherksey states that cells of the invention may be allogeneic to the host, however Cherksey teaches implantation of cells into the brain, an existing immune-privileged site. Cherksey does not teach or suggest the use of RPE cells to create an immune-privileged site and thus, does not teach the claimed invention.

Further, as there is no teaching in Cherksey that RPE cells can create an immune-privileged site, Cherksey provides no motivation for one of skill in the art to modify the teachings therein to arrive at the presently claimed invention.

Still further, since Cherksey describes only implantation of cells into an immune-privileged site, one would have no expectation of success of the present invention from the teaching of Cherksey, *i.e.*, the co-administration of RPE cells with a second cell population wherein the second cell population is allogeneic to the recipient of the cells.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

Goldstein teaches transfecting a tyrosine hydroxylase gene into cells, including RPE cells, and transplanting the genetically altered cells into the brain. Goldstein does not address the fundamental deficiencies of the Office's contention of obviousness and thus the Office has not met its burden to prove obviousness. Goldstein does not teach co-administration of RPE cells with a second cell population. Goldstein contains no disclosure with regard to creating an immune-privileged site with RPE cells. Thus, Goldstein alone or in combination with Cherksey, does not teach or suggest the claimed invention.

Applicants respectfully point out that the cited references do not support *prima facie* obviousness with regard to the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103, to the extent that they are applied to the amended claims.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' agent at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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